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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,358	01/23/2004	Wayne H. Kaesemeyer	126625.00901	7600

7590 04/05/2007

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EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,358	KAESEMEYER, WAYNE H.	
	Examiner	Art Unit	
	Chris E. Simmons	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *14-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/06/2006 03/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement: Receipt of amended claims and Applicant's remarks on restriction requirement is acknowledged.

Election/Restrictions

Examiner required restriction under 35 U.S.C. 121 and 372 to the following inventions:

I. Claim 1-13, drawn to a pharmaceutical composition comprising a nitrate and a biological equivalent of L-arginine or L-citrulline, and

II. Claim 14-21, drawn to a method of treating a subject in need thereof comprising administering a pharmaceutical composition comprising a nitrate and a biological equivalent of L-arginine or L-citrulline.

In addition, the Examiner required an election of species between a pharmaceutical composition comprising a nitrate and a biological equivalent of L-arginine or a pharmaceutical composition comprising a nitrate and L-citrulline. **With traverse,** Applicant elected Group I (claims 1-13) and made a species election of a pharmaceutical composition comprising a nitrate and **L-citrulline**. Applicant, respectfully, argued in remarks received by the Office on 02/21/2007 that the search classification for each invention group will substantially overlap and graciously explained that the specification teaches that citrulline is a biological equivalent of L-arginine. Examiner will respectfully maintain the restriction and make **FINAL** the restriction between Groups I and II. Groups I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another

materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the treatment as claimed can be practiced with materially different products. The inventions between Groups I and II are distinct and will be a serious search burden; therefore, the restriction between Group I and II is proper. However, the Examiner will **WITHDRAW** the election of species requirement after careful consideration of Applicant's persuasive remarks that points out the specification's teaching that citrulline is a biological equivalent of L-arginine.

Priority

1. This application discloses and claims only subject matter disclosed in prior Application No. 09605599, filed 06/28/2000, and names an inventor or inventors named in the prior application. Accordingly, this application may constitute a continuation or division. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78. Priority will not be granted to prior application in Applicant's priority change because they do not teach the claimed combination.

Specification

The Preliminary Amendment dated on 07/28/2004 needs to be corrected.

PCT/US01/20887, filed on 06/28/2001 is claiming priority to U.S. Serial No. 10/258,633 (which has a later filing date of 10/24/2002). Correction is required.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-2, 5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Cohn (US Pat. 4,868,179).

The instant claims are directed to a composition of a biological equivalent of L-arginine and a nitrate.

Cohn teaches in Column 2 Lines 17-20 the "compositions containing hydralazine (a biological equivalent of L-arginine) or a pharmaceutically acceptable salt thereof, and isosorbide dinitrate (a nitrate)".

Any pharmaceutical composition inherently has a pharmaceutically acceptable carrier.

Instant specification teaches that hydralazine and citrulline are biological equivalents of L-arginine. In Applicant's remarks on restriction requirement, Applicant admits that "each of the claims, as presently recited, require a pharmaceutical composition containing a nitrate and a biological equivalent of L-arginine" and that "**citrulline is a biological equivalent of L-arginine**".

4. Claims 1-5 and 8-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Chwalisz et al. (PGPub 2001/0056068 A1).

Chwalisz (in paragraph 91) teaches a composition comprising a nitric oxide donor (defined in paragraph 90 as including isosorbide mononitrate or isosorbide dinitrate) and a nitric oxide substrate (defined in paragraph 16 as L-arginine).

Chwalisz also teaches in paragraph 96, a pharmaceutical composition of either or both of citrulline or citrulline analogue (defined in paragraph 65 as including salts and L-isomers) and a nitric oxide donor.

As stated in instant specification and above, L-arginine is a biological equivalent of hydralazine and L-citrulline.

Any pharmaceutical composition inherently has a pharmaceutically acceptable carrier. However, Chwalisz teaches that above composition can be administered in admixture with conventional excipients (in paragraph 112).

5. Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Schneider et al.

Schneider et al. teaches a composition comprising a nitric oxide donor (isosorbide dinitrate) and nitric oxide substrate (L-arginine or a salt thereof) in claims 2-3, and 14 a composition comprising a salt of L-arginine and a nitrate.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 3-4 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohn (US Pat 4,868,179) in view of De Lucchi et al. (United States Patent 4,713,466).

Instant claims are directed to a composition comprising a biological equivalent of L-arginine and a nitrate (specifically isosorbide 5 mononitrate).

Cohn teaches a composition comprising hydralazine (a biological equivalent of L-arginine) and isosorbide dinitrate (a nitrate).

Cohn does not teach isosorbide mononitrate.

De Lucchi et al. (Background paragraph 2) teaches isosorbide 5 mononitrate is a metabolite of isosorbide dinitrate.

It would have been obvious to one of ordinary skills in the art to combine De Lucchi et al. to Cohn to replace the dinitrate in Cohn with its mononitrate metabolite and to replace L-arginine with its biological equivalent, citrulline.

One would have been motivated to make the above changes with the expectation of isosorbide dinitrate (ISDN) and isosorbide-5-mononitrate exhibiting an analogous pharmacological action. However, isosorbide-5-mononitrate has the following advantages:

(a) In the metabolic process it provides only one mole of nitric acid instead of two.

(b) In contrast to ISDN which metabolises into its two mononitrate isomers, it consists of a single active substance rather than three substances, the concentration ratios and thus the activities of which vary mutually with time.

(c) It undergoes much slower metabolism and therefore exhibits a more lasting action.

(d) It becomes distributed not only within the plasma but also throughout a much wider extent which can be approximated to that of the total body water.

One would have been motivated to make the above changes with the expectation of citrulline (the biological equivalent of L-arginine) and L-arginine exhibiting an analogous pharmacological action.

Conclusion

1. References that are pertinent to current application but not relied upon for rejection:

   Cooper, (US Pat. 4,557,934 A)

2. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chris E. Simmons whose telephone number is (571) 272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on (571) 272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chris Simmons/CES

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER